

**REMARKS**

Claims 1-4, 10-22, and 23-25 were pending. Claim 1 has been amended to make explicit that the amino acid residue corresponding to Ser-63 is replaced with a lysine residue and the residue corresponding to Arg-192 is replaced with an asparagine or glycine residue (see, e.g., page 8, lines 20-24). Accordingly, claims 20-22 have been canceled without prejudice or disclaimer.

Thus, claims 1-4, 10-19, and 23-25 are pending as shown above. Claims 10-18 and 24 are withdrawn as being drawn to non-elected inventions and claims 1-4, 19, 23, and 25 are under active consideration.

**35 U.S.C. § 102**

Claims 1-4, 19-21, 23, and 25 remained rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by the reference of Domenighini et al. (International Patent Application WO 93/13202; hereinafter "Domenighini") in view of evidence provided by Pizza et al. (Mol. Microbiol. (1994) 14:51-60). In particular, the Office continues to allege that Domenighini discloses an immunogenic detoxified protein comprising the amino acid sequence of subunit A of an *Escherichia coli* heat labile toxin (LT-A) having the mutations Ser63Lys and Arg192Asn and a vaccine composition comprising this protein (Advisory Action, page 2).

Applicants respectfully traverse the rejection.

For a reference to anticipate claimed subject matter under 35 U.S.C. § 102, "the reference must teach every aspect of the claimed invention either explicitly or implicitly." M.P.E.P. § 706.02. Applicants respectfully submit that Domenighini does not teach all aspects of the Applicants invention, either explicitly or implicitly.

Domenighini fails to describe or demonstrate that an LT-A protein having both the amino acids at the position corresponding to Ser-63 and Arg-192 replaced with the indicated amino acids is immunogenic and detoxified as currently claimed. Domenighini provides a list of single mutants – there is no description or demonstration of double mutants as claimed in that no double mutants are actually made or tested.

Moreover, Domenighini teaches that Arg-192Asn mutation does absolutely nothing to reduce toxicity. See, Row O of Table I. Accordingly, it is not inherent in the reference that a double mutant with this mutation would exhibit reduced toxicity as claimed.

Therefore, claim 1 and all claims dependent therefrom are not anticipated by Domenighini, and withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested.

**35 U.S.C. § 103**

Claim 22 was rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Domenighini et al. (*supra*) in view of the reference of Clements et al. (U.S. Patent No. 6,019,982; hereinafter "Clements"). Claim 22 has been canceled; however, limitations of claim 22 have been incorporated into claim 1. Accordingly, this rejection will be addressed with respect to claim 1. Domenighini is cited for teaching DNA molecules that encode mutant detoxified heat labile toxin of *E. coli* and mutant detoxified cholera toxin having mutations in the A subunit at positions 63 and 192. The Office acknowledges that Domenighini fails to disclose an Arg192Gly mutation. Clements was cited for teaching the Arg192Gly mutation.

Applicants respectfully traverse the rejection under 35 U.S.C. § 103 and the Office Action remarks and purported facts underlying the rejection on the following grounds.

As set forth by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727; 82 USPQ2d 1385, 1397 (2007) and Patent Office Guidelines regarding determining obviousness issued in view of *KSR*, an obviousness rejection is only proper when the proposed combination of elements results in a predictable outcome (see, Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in view of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, Fed. Reg. Vol. 72, No. 195, October 10, 2007, emphasis added):

The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one or ordinary skill in the art at the time of the invention.

Rather, the Supreme Court in *KSR* reiterated that an obviousness inquiry is fact-dependent and that “a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR*, 82 USPQ2d at 1389. The Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references. See, e.g., *In re Kotzab*, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000).

Thus, a rejection cannot be predicated on the mere identification of individual components, in this case particular single mutants, of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed subject matter, would have selected and modified these components for combination in the manner.

In the instant case, there is no evidence supporting the assertion that Domenighini or Clements establish anything about the predictable use of double mutants. Clements is admittedly silent as to double mutants and Domenighini does not make or test even one double mutant, and certainly not the particular double mutants as claimed. Moreover, Domenighini teaches that mutating the Arg192 residue does not result in reduced toxicity. Thus, it is not predictable from either reference that double mutants would function as claimed as it is not predictable from single mutations what functional characteristics double mutants might have.

Therefore, the Office has failed to provide evidence that the claimed invention is a “predictable use of prior art elements according to their established functions.” In fact, the evidence is to the contrary. The cited art fails to provide evidence that a mutated CT-A or LT-A protein comprising the combined substitutions at the position corresponding to Ser-63-Lys and the position corresponding to Arg-192-Asn/Gly would not only retain

immunogenicity, but also be detoxified and more resistant to trypsin proteolysis than wild type CT-A or LT-A.

The primary reference of Domenighini fails to disclose all of the elements of the pending claims, namely an immunogenic detoxified LT-A protein having amino acid substitutions at both Ser-63-Lys and Arg-192-Gly/Asn. Moreover, Domenighini teaches that an Arg192Asn mutant was not known to be detoxified. (see Table I at page 46).

Clements also fails to teach it was in any way predictable that double mutants would have the claimed characteristics. In view of the clear teaching by Domenighini that mutation of position Arg192 did not detoxify the protein and Clements' failure to teach multiple mutations, one of skill in the art would have had no reason to combine Clements and Domenighini to arrive at the claimed invention and a *prima facie* case of obviousness cannot be established or sustained.

For at least these reasons, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

**35 U.S.C. § 112, first paragraph, enablement**

Claims 1, 3, 4, 19, 23, and 25 were again rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not provide an enabling disclosure commensurate in scope with the claims.

In view of the foregoing amendments specifying the amino acid residue replacements, withdrawal of the enablement rejection under 35 U.S.C. § 112, first paragraph, is in order.

**CONCLUSION**

In light of the above remarks, Applicants submit that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned.

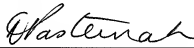
The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

Please direct all further written communications regarding this application to:

Silvia Brazzini  
Novartis Vaccines & Diagnostics, Inc.  
Intellectual Property – X-100B  
P. O. Box 8097  
Emeryville, CA 94662-8097  
Tel: (510) 923-2708  
Fax: (510) 655-3542

Respectfully submitted,

Date: October 27, 2008

By: 

Dahna S. Pasternak  
Registration No. 41,411

Novartis Vaccines & Diagnostics, Inc.  
Intellectual Property – X-100B  
P. O. Box 8097  
Emeryville, CA 94662-8097